2) This invention relates to transgenic animals.

(3) It is possible to insert foreign genes into vertebrate embryos, and for these genes to be incorporated into the genome of the resulting animal. Insertion of the foreign genes has been carried out mechanically (by microinjection), and with the aid of retrovirus vectors (for example, as is described in Huszar et al. (1985) P.N.A.S. U.S.A 82, 8587). The animals resulting from this process are termed "transgenic." The foreign genes can be sexually transmitted through subsequent generations and are frequently expressed in the animal. In some instances the proteins encoded by the foreign genes are expressed in specific tissues. For example, the metallothionein promoter has been used to direct the expression of the rat growth hormone gene in the liver tissue of transgenic mice (Palmiter et al., 1982 Nature 300:611). Another example is the elastase promoter, which has been shown to direct the expression of foreign genes in the pancreas (Ornitz et al., 1985 Nature 313:600). Developmental control of gene expression has also been achieved in transgenic animals, i.e., the foreign gene is transcribed only during a certain time period, and only in a particular tissue. For example, Magram et al. (1985, Nature 315:338) demonstrated developmental control of genes under the direction of a globin promoter; and Krumlauf et al. (1985, Mol. Cell. Biol. 5:1639) demonstrated similar results using the alpha-feto protein minigene.

(4) SUMMARY OF THE INVENTION

(5) In general, the invention features a DNA sequence containing a gene encoding a protein, the gene being under the transcriptional control of a mammalian milk protein promoter which does not naturally control the transcription of the gene, the DNA sequence further including DNA enabling secretion of the protein; e.g., a secretion signal-encoding sequence

interposed
between the gene and promoter. The promoter can be that of a milk serum
protein or a casein protein, although milk serum proteins are preferred, as
will be discussed in more detail below. (As used herein, "gene" refers to both
genomic DNA sequences and cDNA sequences.)

(6) The invention permits the production of any desired protein in an easily
maintained stable, portable culture system, i.e., a living domesticated mammal,
which is capable not only of producing the desired protein, but preferably of
passing on the ability to do so to its female offspring as well. Secretion of
the protein into the host mammal's milk facilitates purification and obviates
removal of blood products and culture media additives, some of which can be
toxic or carcinogenic. More importantly, protein yields will be high and
production will be more cost effective and efficient.

(7) Other features and advantages of the invention will be apparent from the
following description of the preferred embodiments thereof, and from the
claims.

(8) DESCRIPTION OF THE PREFERRED EMBODIMENTS

(9) The drawings will first briefly be described.

DETAILED DESCRIPTION:

(1) DRAWINGS

(2) FIG. 1 is a diagrammatic representation of the construction of an
intermediate vector of the invention, pt-PA VP1-LP(K).

(3) FIG. 2 is a diagrammatic representation of the construction of an
intermediate vector of the invention, pWAP (H.sub.3).

(4) FIG. 3 is a diagrammatic representation of the construction of a vector
of the invention, pWAP-t-PA(S).

(5) FIG. 4 is a diagrammatic representation of the construction of an intermediate vector of the invention, pHbsSVA.

(6) FIG. 5 is a diagrammatic representation of the construction of a vector of the invention, pWAP-Hbs(S).

(7) DNA SEQUENCE ELEMENTS

(8) Promoter

(9) The milk protein promoter can be derived from any mammalian species, and can be any promoter naturally associated with any protein which is normally secreted into mammalian milk. Generally, milk proteins are classified as the caseins, which are defined herein as the milk proteins which are present in milk in the form of micelles, and which are removed from skim milk by clotting with rennet; and the milk serum proteins, which are defined herein as the non-casein milk proteins. Whey proteins constitute the predominant fraction of the milk serum proteins, and in rodents include the protein known as whey acid protein. Whey acid protein ("WAP") is named based on its acidic isoelectric point (Piletz (1981) J. Biol. Chem. 256: 11509). Another example of a milk serum protein described in the literature is .alpha.-lactalbumin (described, along with mouse WAP, in Hennighausen and Sippel (1982) Eur. J. Biochem. 125, 131). Milk proteins are discussed in detail in Walstra and Jenness Dairy Chemistry and Physics (John Wiley & Sons 1984).

(10) Generally, milk serum protein promoters are preferable to casein promoters in the present invention because caseins generally are produced in female mammals during pregnancy as well as after birth, while WAP is expressed primarily during post-partum lactation. This difference is of potential importance for two reasons. First, pre-birth production of the

we turn first to the knowledge and skill of the art with regard to the small genus (about 7 types of promoters) of milk promoters and then to the skill in the art, especially with regard to the manipulation of promoters or sequences which include such promoters. Appellant specifically points out that it is not making an enablement-based argument for the satisfaction of the written description requirement (as was made by Fiers in Fiers v. Revel) but is conducting the review of the level of skill and knowledge required for a written description analysis, as mandated by the Guidelines.

As is discussed above, the Examiner has ignored this requirement and has ignored the fact that the art has so well characterized numerous milk specific promoters that one can, with this knowledge provided in the art, show possession of the invention. The Examiner has ignored the teachings of the art, formulated her own way of distinguishing milk specific promoters (the identification of a special motif) and demanded that that formulation be satisfied, even when the art itself provides a different and fully satisfactory way of identifying milk specific promoters and distinguishing them from other promoters.

We now turn to specific examples, drawn from the art, of the "skill and knowledge" in the art. We will first discuss the promoter regions themselves and then discuss general methods for manipulating and using eukaryotic promoters.

i. The level of skill and knowledge in the art with regard to sequences which include a milk promoter

The genus of milk protein promoters was well characterized and defined in the art at the time of filing. This is shown by the five references (all published prior to the filing date of the instant application) discussed below.

These references provide: the cloned genomic sequence, identify the 3' end of the 5' regulatory region, identify characteristic 5' regulatory structures, and provide a significant amount of DNA sequence for the promoter regions, of each of five of the seven types of milk promoters. Appellant notes that information from three different species, rat, mouse, and bovine was in the art at the time of filing. The disclosure of the references is summarized in Table 1.

(1) Table 1. Summary of Milk Promoter Information in Art at the Time of Filing

	Milk Serum Proteins			Caseins			
	α-lact-albumin[1]	β-lactoglobulin	Whey Acid Protein[2] (WAP)	α-casein[3]	β-casein[4]	γ-casein[5]	κ-casein
5' flanking regions cloned in the art?	Yes, 8.5 kb	-	Yes, 9 kb	Yes, 7.1 kb	Yes, 14.6 kb	Yes, 9 kb	-
Restriction Analysis provided in the	Yes	-	Yes	Yes	Yes	Yes	-

art?							
3' end of regulatory region determined in the art?	Yes	-	Yes	Yes	Yes	Yes	-
Promoter region nucleotide sequence data provided in the art?	1,247 bps	-	1,175 bps	680 bps	780 bps	90 bps[5]; 680 bps[3]	-
5' structures, e.g., TATA or CAAT boxes, identified?	Yes	-	Yes	Yes	Yes	Yes	-
RNA transcription start site and sequences preceding that site identified?	Yes	-	Yes	Yes	Yes	Yes	-
Glucocorticoid receptor binding sites, or hormone receptor binding sites	Yes	-	Yes	-	Yes	Yes	-

1. Qasaba and Safaya (1984), *supra.*
2. Campbell *et al.* (1984), *supra.*
3. Yu-Lee *et al.* (1986), *supra.*
4. Jones *et al.*. (1985), *supra.*
5. Yu-Lee and Rosen (1983), *supra.*